DETAILED ACTION

1. Claims 1-13 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-12) in the reply filed on 2/29/08 is acknowledged.

Claim 13 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/29/08.

3. Applicant's election without traverse of test species for organic anion transporter inhibitor and estrone-3-sulfate transporter species for SLC transporter in the reply filed on 2/29/08 is acknowledged.

4. Claims 1-12 are all the pending claims under examination.

Priority

5. Receipt is acknowledged of papers (the certified copy of the Japanese language priority document 2003-177021 (filed 6/20/03)) submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. However, because a certified translation has not been filed, the instant claims are given benefit of priority to the international filing date of 6/18/04 for PCT/JP04/08958.

Information Disclosure Statement

6. The U.S. PGPub, the two foreign patent references and the three non-patent literature references cited in the IDS of 12/19/05 have been considered and entered. The Japanese language WO 01/21792 application is acknowledged as the international priority document for the English language EP 1223217 document. The copy of the examiner's initialed 1449 form is attached.

Specification

7. The disclosure is objected to because of the following informalities:

a) The specification fails to cross-reference related applications (MPEP §201.11).

b) The figure legend for Figure 8 on p. 12 at lines 2-7 of the specification is objected to for failing to identify the two panels and for failing to identify the meaning of the lanes labeled A-F and 8 in the top panel and lanes 1-4 in the bottom panel.

Appropriate correction is required.

Claim Objections

8. Claims 8-12 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n).

Accordingly, claims 8-12 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-7 are indefinite for the recitation "measuring/evaluating" in Claims 1, 2, 3, 4 and 5 because the meaning of the phrase is not clear. The art recognizes the method step of "measuring" and the method step of "evaluating" to be quite different and perhaps even occurring at different points in the method. The two on-line definitions for "measuring" from Stedman's Medical Dictionary and Merriam-Webster Dictionary, and the two on-line definitions for "evaluating" from Stedman's Medical Dictionary and Merriam-Webster Dictionary are attached. The ordinary artisan would understand the terms to represent separate steps, where the measurement took place followed by the evaluation of whether the data from the measurement correlated with some outcome, i.e., a breast cancer remedy.

b) Claims 2 and 3 are indefinite for reciting a broadening limitation for "transporter activity" whereas Claim 1 is drawn to "an estrone-3-sulfate transporter." Alternatively, the claims are lacking in antecedent basis for the phrase "transporter activity" because Claim 1 does not indicate that "uptake activity" is the same as or related to "an estrone-3-sulfate transporter."

c) Claim 7 is indefinite for the recitation "or a cell line derived therefrom" because it is not clear what genotypic and/or phenotypic features or characteristics for either of the MCF-7 or T-47D cell lines the corresponding derivative would possess, other than presumably expressing an estrone-3-sulfate transporter. The specification does not define a derivative or how to make a derivative for any of these cell types.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

10. Claim 7 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

It is unclear if a cell line which is a *derivative* of an MCF-7 cell line or a *derivative* of a T-47D is known and publicly available, or can be reproducibly isolated without undue experimentation. The ATCC website lists deposits and accession nos. for the parent MCF-7 and T-47D cell lines. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell lines; or (2) a cell line which expressed an estrone-3-transporter derived from the MCF-7 or T-47D cell lines would require undue experimentation. Deposit of the cell lines derived from the MCF-7 cell line or the T-47D cell line would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record

who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Enablement

11. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for practicing the method using a breast cancer cell line, e.g., MCF-7 or T-47D, expressing an estrone-3-sulfate transporter in order to make a correlation between a test substance as a candidate for modulating estrone-3-sulfate binding and/or transport into cells for breast cancer therapy, does not reasonably provide enablement for using just any cell lines expressing an estrone-3-sulfate

transporter without there being some correlation between the cell line and breast cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to screening drug test candidates which effect uptake of estrone-3-sulfate by any cell expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 1), or to screening drug test candidates which effect binding of estrone-3-sulfate to any cell membrane fraction expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 4), or to screening drug test candidates which effect uptake of estrone-3-sulfate to any cell membrane vesicle expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 5).

The relative skill required to practice the method is a clinical technician with a background in receptor binding assays and breast cancer diagnostics.

Disclosure in the Specification/ Prior Art

The specification teaches that estrone-3-sulfate is taken up by estrogen-dependent T-47D cells expressing an estrone-3-sulfate transporter and uptake can be inhibited by DHEAS steroid hormones, bromosulfophthalein and taurocholic acid, whereas estradiol-17β-glucuronide, salicylate, p-aminohippuric acid, tetraethylammonium, cyclosporin A, and digoxin were not inhibitory (Table 1); and that the OATP and OAT transporters are candidate transporters although the exact transporter for the breast cancer cell line T-47D was not identified.
Nezu et al. (EP 1223217; published 7/17/02; filed 9/20/00; cited in the IDS of 12/19/05) teach expression of the SLC (OATP) transporter protein in mammary cancer cell line (GI-101) [0123]. Pasqualini et al. (Can Lett. 66:55-60 (1992); cited in the IDS of 12/19/05) teaches estrone-3-sulfate transporters are inherent to the human breast cancer MCF-7 or T-47D cell lines.

Unpredictability/Undue Experimentation

The specification is not enabling for using just any cell lines expressing any estrone-3-sulfate transporter in order to screen for breast cancer drug therapy candidates. One skilled in the art could not practice the screening method using any cell line that was not known to have a recognized clinical correlation with human breast cancer. One skilled in the art could not practice the screening method using just any cell line that was able to transport estrone-3-sulfate into the cell because as Applicants

teach in their own specification, there are several classes of transporters, and different cell types expresses these transporters. Thus the specificity and reliability of the cell-based assay would not be precisely correlated with breast cancer cell mechanisms using anything but a human breast cancer cell line known to have an estrone-3-sulfate transporter on its cell surface.

One skilled in the art would be required to practice undue experimentation to practice the method using anything other than an art-recognized human breast cancer cell line possessing all these features. Further, one skilled in the art could not practice the method invention with any cell line derived from the MCF-7 or T-47D cell lines in the absence of knowing how to derivatize the parent cell lines, what characteristics the derivatized cell lines should possess or how the cell lines would perform under the identical assay conditions as taught in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1, 2, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Pasqualini et al. (Can Lett. 66:55-60 (1992); cited in the IDS of 12/19/05).

Claims 1, 2, 6 and 7 are interpreted as being drawn to screening drug test candidates which effect uptake of estrone-3-sulfate by any cell expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 1), where the concentration of estrone-3-sulfate in the cell is reflective of whether the test compound inhibits the transporter activity (Claim 2), or where the estrone-3-sulfate transporter is expressed on a human breast cancer cell line (Claim 6),and where the breast cancer cell line is MCF-7 or T-47D (Claim 7).

Pasqualini teaches that the human breast cancer cell lines, MCF-7 or T-47D, express a functional estrone-3-transporter and that estrone-3-sulfate transport and conversion to estrone is involved in the pathogenesis of the breast cancer. Pasqualini teaches methods for measuring the effects on two drugs, R5020 or progesterone, in changing uptake of estrone-3-sulfate by culturing the cell lines in vitro with the organic compound and the test drugs to see whether uptake is inhibited (Figure 1).

13. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Nezu et al. (EP 1223217; published 7/17/02; filed 9/20/00; cited in the IDS of 12/19/05).

Claims 1-3 and 6 are interpreted as being drawn to screening drug test candidates which effect uptake of estrone-3-sulfate by any cell expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 1), where the concentration of estrone-3-sulfate in the cell is reflective of whether the test compound

inhibits the transporter activity (Claim 2), or where the level of cell proliferation is reflective of whether the test compound inhibits the transporter activity (Claim 3), or where the estrone-3-sulfate transporter is expressed on a human breast cancer cell line (Claim 6).

Nezu teaches methods of screening for a test compound that promotes or suppresses the transporter activity of the SLC (OATP) transporter protein, comprising the steps of:(a) providing a cell that expresses the SLC (OATP) transporter protein on the cell membrane; (b) contacting a test compound and a labeled organic compound to be transported through the intermediary of the SLC (OATP) transporter protein with the cell; (c) measuring the amount of the labeled organic compound that has been taken up into said cell; and (d) selecting-the test compound that increases or decreases the amount of the labeled organic compound taken up into said cell as compared with that observed in the absence of the test compound (control) (Claim 10), where the organic compound is estron-3-sulfate [0020; 0115] and the test compound is measured for its ability to change the uptake and concentration of the organic compound or the proliferation of cells [0113], and drug selection is based on these criteria. Nezu teaches the expression of the SLC (OATP) transporter protein in mammary cancer cells (GI-101) [0123]. Thus based on the teachings of Nezu, one skilled in the art could readily use the human mammary cancer cell line, GI-101, in the method assay for screening for drugs that would effect the transport of estrone-3-sulfate by the SLC (OATP) transporter protein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nezu et al. (EP 1223217; published 7/17/02; filed 9/20/00; cited in the IDS of 12/19/05) in view of Suzuki et al. (Jap. Pharm. & Therap. 30 (Suppl. 2):S433-S436 (2002); Abstract only).

Claim 4 is interpreted as being drawn to screening drug test candidates which effect binding of estrone-3-sulfate to any cell membrane fraction expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy. Claim 5 is interpreted as being drawn to screening drug test candidates which effect uptake of estrone-3-sulfate to any cell membrane vesicle expressing an estrone-3-sulfate transporter in order to identify a breast cancer therapy (Claim 5).

The claimed method of using cell membrane extracts or cell membrane vesicles containing estrone-3-sulfate transporter proteins for drug screening was prima facie obvious at the time of the invention over Nezu and Suzuki.

Nezu teaches methods of screening for a test compound that promotes or suppresses the transporter activity of the SLC (OATP) transporter protein, comprising the steps of:(a) providing a cell that expresses the SLC (OATP) transporter protein on the cell membrane; (b) contacting a test compound and a labeled organic compound to be transported through the intermediary of the SLC (OATP) transporter protein with the cell; (c) measuring the amount of the labeled organic compound that has been taken up into said cell; and (d) selecting-the test compound that increases or decreases the amount of the labeled organic compound taken up into said cell as compared with that observed in the absence of the test compound (control) (Claim 10), where the organic compound is estron-3-sulfate [0020; 0115] and the test compound is measured for its ability to change the uptake and concentration of the organic compound or the proliferation of cells [0113], and drug selection is based on these criteria. Nezu teaches the expression of the SLC (OATP) transporter protein in mammary cancer cells (GI-101) [0123]. Thus based on the teachings of Nezu, one skilled in the art could readily use the human mammary cancer cell line, GI-101, in the method assay for screening for drugs that would effect the transport of estrone-3-sulfate by the SLC (OATP) transporter protein. Nezu does not teach using membrane extracts or memebrane vesicles comprising the transporter protein in the drug screening assay, but Suzuki rectifies this deficiency.

Suzuki discloses using membrane vesicles comprising the breast cancer resistance protein (BCRP) which regulates estrone-3-sulfate uptake into the vesicles. Suzuki teaches that the vesicles can be used to the monitor the effects of different drugs on estrone-3-sulfate uptake where sulfate conjugates were shown to suppress uptake. Inherent to preparation of the vesicles would have been the use of membrane fractions (natural or synthetic) in order to render the BCRP protein available for interacting with estrone-3-sulfate.

One skilled in the art would have been motivated and been reasonably assured of success in having produced the membrane fractions or membrane vesicles comprising the estrone-3-sulfate transporter over Nezu and Suzuki at the time of the invention. Each of the references teaches and appreciates assays for screening drug effects on estrone-3-sulfate transport vis-à-vis specific estrone-3-sulfate transporter, where the SCL protein of Nezu or the BCRP protein of Suzuki could readily have been used in the assay format as a membrane fraction or membrane vesicle in order to reduce any non-specific uptake or signal/noise ratio and to selectively identify the drug interaction(s) with estrone-3-sulfate or the estrone-3-sulfate transporter. One skilled in the art would have been reasonably assured of success in having produced either the membrane fractions or membrane vesicles of Suzuki and applied them to the drug screening methods of Nezu because the reagents were available at the time of the invention, and Suzuki had shown specific drug inhibition of estrone-3-sulfate uptake into vesicles comprising membrane components as an alternative to whole cell methods of

Nezu. For the foregoing reasons, the claimed methods were prima facie obvious at the time of the invention.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/

Examiner, Art Unit 1643
Temporary Partial Signatory Authority